Eco-friendly peptide synthesis

A doctoral candidate in biochemistry at TU Darmstadt has almost by accident come across a method which makes the manufacturing of peptides more ecological and cheaper. A company is to emerge from the business idea.

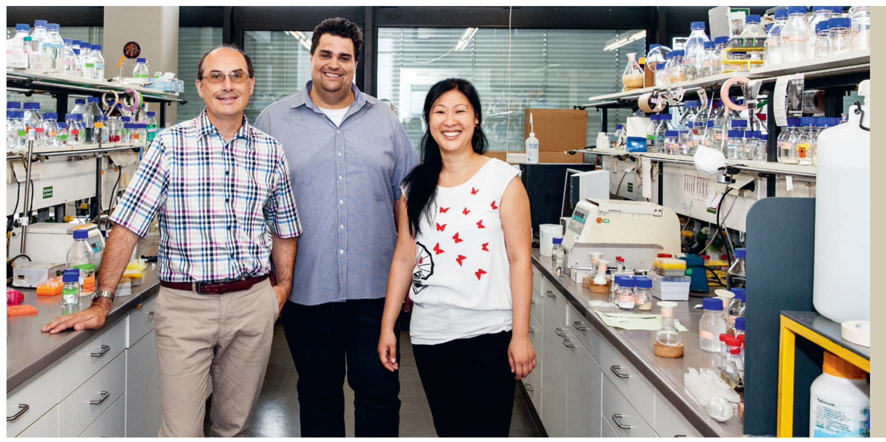

Photo: Sandra Junker

The team behind Sulfotools GmbH: Harald Kolmar, Sascha Knauer and Christina Uth (from the left).

By Uta Neubauer

Sascha Knauer, a doctoral candidate in Professor Harald Kolmar's team in the institute of biochemistry, was actually dealing with nanoparticles. But around a year ago, he made a chance discovery while supervising a diploma student making the manufacturing of peptides – chain-shaped biomolecules consisting of amino acids – considerably more environmentally friendly.

Knauer changed the topic of his thesis, applied for a patent and gained his colleague Christina Uth, also a graduate engineer and doctoral candidate in biochemistry, as business partner. He intends to found the Sulfotools GmbH with her this year. Doctoral supervisor Kolmar participates as a founder, but will leave the operational business to Knauer and Uth.

Knauer's thesis now bears the provisional title "Merrifield reloaded". What sounds more like the remake of a movie or a band to a layperson refers to the Merrifield synthesis which connects amino acids to peptides. The American chemist Robert Bruce Merrifield was awarded the Nobel Prize in 1984 for developing this method.

Despite the award, the process implicates a number of intrinsic drawbacks, most important the use of the organic solvent dimethylformamide – the industry requires about 13,000 tons each year solely for the production of active peptide ingredients for therapeutics.

Peptides are also used in cosmetics and in food supplements. The high solvent usage is not only unsafe for the environment, but makes the manufacturing process complex and expensive, particularly because the products must be thoroughly purified from solvent residues. After all, no one wants to swallow dimethylformamide residues or rub them onto their skin.

All efforts to carry out peptide synthesis in water instead of organic solvents failed until now. The crucial point: For the correct combination, the amino acids must be provided with protecting groups. As a result, they become extremely insoluble in water. However, when the Diploma student supervised by Knauer manufactured peptide components in the presence of sulphuric acid, water-soluble protecting groups were formed as by-products of the reaction. Knauer recognized the potential: With these protecting groups, the Merrifield synthesis works in water. The business idea was born.

The Darmstadt-based academics have already synthesized some short peptides using their modified technology. The proof-of-principle has been demonstrated; now the process should be validated and optimized. "We are in discussions with various industrial partners and are now concentrating on commercially relevant peptides," Uth says.

Besides substituting organic solvents with water, the new method has additional benefits, Knauer emphasizes: "We have optimized the entire process." Cost savings of up to 50 percent are possible, as the use of chemicals can be drastically reduced and the purification of the products is easier.

No question - the idea has potential, since the market for peptides is growing. In Germany's start-up contest Science4Life Venture Cup 2015, the Sulfotools team just recently took second place and was awarded 10,000 euro.

The author is an academic journalist with a PhD in chemistry.

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hoch³ FORSCHEN
SCIENCE QUARTERLY
Autumn 2015
TECHNISCHE UNIVERSITÄT DARMSTADT

Imprint

Publisher
President of TU Darmstadt,
Karolinenplatz 5,
64289 Darmstadt,
Germany

Editor
Corporate Communication
Jörg Feuck (Editor-in-chief)
Ulrike Albrecht (Graphic Design)
Patrick Bal (Images)

Conceptual design
conclouso GmbH & Co. KG,
Mainz, Germany

Photography (title)
Sandra Junker

Circulation
6.000

Next issue
16th of December 2015

Service for readers
presse@pvw.tu-darmstadt.de

Newsletter subscription
www.tu-darmstadt.de/newsletter

ISSN
2196-1506

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Banking on uncertainties

Computer simulations are only as good as the input data on which they are based. They are more reliable if the uncertainties are considered in the core data.

By Hildegard Kaulen

Everyone knows intellectual games. You wonder what could happen, assume certain presumptions and requirements, run through various scenarios and solutions in your head and become more accurate the more precise the actualities of the situation are considered. Professor Dr. Sebastian Schöps and Dr. Sebastian Ullmann from TU Darmstadt basically do nothing else for computer-based engineering sciences. They develop software programs with which you can simulate the attributes and operation of complex systems and their environmental conditions. In developing the software, they concentrate on two specifications: The programs should map reality as accurately as possible so that the models and simulations are subsequently reliable and the programs should be quick. "In an industrial company, a complex simulation must not last longer than one night," Schöps says. "It is best if the result is already available after a coffee break."

„We intend to ensure that manufacturers can consider the impacts of uncertainties in their design from the outset."

Schöps and Ullmann, together with Professor Dr. Jens Lang, lead the profile topic "Uncertainty Quantification" at the graduate school of "Computational Engineering". This pools and coordinates the relevant activities at the TU Darmstadt. Schöps has been junior professor in the department of Electrical Engineering and Information Technology in Darmstadt for three years. Ullmann is a mathematician and has been early career research group leader at the "Computational Engineering" graduate school for the past year. Lang is also a mathematician and has been a professor in Darmstadt for 14 years. People interested in algorithms come, among other things, from industry because ever more companies would like to simulate and assess the attributes and use of their products using computers today. This approach is cheaper than endless practical tests and speeds up development cycles. Both conditions are important competitive factors.

Any computer model and any simulation is, however, only as good as its input data. As this is almost always subject to uncertainties, these are also taken into consideration in model development and simulation. A distinction is made between two types of uncertainty: Those based on coincidences and those concerned with a lack of knowledge. Random uncertainties are, for example, manufacturing defects or inaccuracies in measurement. Neither can ever be entirely excluded. Uncertainties based on knowledge gaps may, on the other hand, be reduced by further data. "By quantifying the uncertainties – what is known as the Uncertainty Quantification – we can calculate the effect of random disruptions to the simulation result," Ullmann explains. "As a result, the simulations are more reliable and more practical for everyday use. We intend to get as close as possible to reality using our software programs."

By taking uncertainties into consideration, a product will be more robust. Schöps explains what is meant by this: "Electrical machines or components may react very well under optimum conditions; with slight deviations from this, however, show sharp declines. We try to quantify such performance losses in good time so that, when manufacturing or further developing the products, the manufacturers are able to approach the feasibility limits more closely without having to worry about negative consequences." In the simulations, Schöps and his colleagues therefore let themselves be guided by questions such as: What are the sensitive components of a machine? What happens if the geometry or the material of components is altered? Or: Can you have certain parts made from a cheaper material without having to worry about reduced capacities due to any fluctuations? "We intend to ensure that manufacturers can consider the impacts of uncertainties in their design from the outset," Schöps says. "Products will then no longer have to be oversized and will be less expensive."

The uncertainties are calculated using numerical methods. The best known is the Monte Carlo Method.

Photo: Katrin Binner

Developing specific software for complex simulation: Professor Dr. Sebastian Schöps (r.) and Dr. Sebastian Ullmann.

This method is, however, very time-consuming because thousands of randomly generated model options must be simulated for it. "Depending on the problem, this can take a week or longer," Ullmann says. "The users do not have this time. We are therefore developing more efficient calculation methods." Ullmann and his colleagues are working on polynomial chaos methods. These methods use the mathematical attributes of simulation results in order to reduce the number of simulations required. They assume that the results depend like polynomials on random data. "As a result we can save simulations without having to put up with losses in accuracy," Ullmann explains.

Because it is always about practical relevance, the results flow into a whole series of industrial projects which are processed together with external partners. For example, the researchers make simulations which are suitable for making the engine of an e-bike cheaper, enhancing the performance of a particle accelerator and improving the durability of semiconductors. Schöps has also coordinated the German collaborative research consortium SIMUROM for two years in which Professor Dr. Stefan Ulbrich is also involved in his research group of Non-linear Optimization and which deals with uncertainties and more robust optimization throughout the university. Computational engineering is a relatively young discipline and has quickly established itself as the third pillar alongside theory and experimentation in the engineering sciences. The TU Darmstadt is taking on a pioneering role in this field with its course of studies of Computational Engineering and its associated graduate school.

The author is an academic journalist with a PhD in biology.

Graduate School of Computational Engineering at the TU Darmstadt

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Who is driving then?

Professor Hermann Winner and Walther Wachenfeld from the Institute of Automotive Engineering illustrate the opportunities, risks and challenges of autonomous driving.

Interview: Jutta Witte

Professor Winner, Mr. Wachenfeld, when will the first autonomous cars drive in regular traffic?
Winner: There will be no vehicle which is autonomously on the road everywhere at all times even in the next thirty years. These vehicles currently move back and forth on a trial basis in a specific network and are constantly monitored. So, the vision of a vehicle which reacts intelligently in any situation will not occur so quickly; highly automated driving on certain routes, however, yes.

What does this mean?
Wachenfeld: That the driver will have to take over the steering wheel if necessary, but may also deal with other things, for example process emails without paying attention to traffic – whilst the system prompts acceptance. So, at this configuration level, the driver will not yet be completely released and able to fold down the steering column and sleep.

What would be a typical situation in which the onboard computer prompts the driver to take over?
Wachenfeld: With today's assistance systems, the driver is prompted if, for example, breaking needs to take place above a specified level or steering needs to take place beyond a specific power. And the lower accident rates using these assistance systems show that people can actually control this well technically. In the case of highly automated vehicles, however, one no longer counts on intervention by people in this form. A highly automated car must, for example, be capable of making an emergency stop and then always apply this when necessary. High automation does not have the option of doing nothing. This is one of the technical challenges that we now face.

Will autonomous driving further reduce accidents?
Winner: An argument in favour of the need for implementation is very clear that the risk of accidents drops due to autonomous driving. After all, people cause the majority of accidents. So, safety is a major topic in the inter-relationship. One must, however, also see that any new system which has an influence on traffic produces new problems. It is, however, important that the end result is positive.

Do robots drive more safely than people then?
Winner: It is extremely difficult to prove that.

Can a machine react to situations as a person does or are there limits which cannot be resolved technically either?
Winner: We do not know these limits yet, to be honest. But we do know that machines will drive differently from people. Caution will be the main criterion, especially in the infancy of autonomous driving: Distances and speeds, for example, must be precisely met. Driving will be very defensive – untypical of people. And there will be obvious weaknesses: Machines will certainly not master anticipation in traffic so well, just as little dealing with exceptional situations. And nobody knows exactly whether the one will compensate for the other at the moment.

Is this not also an ethical problem?
Winner: This has been discussed many times, in particular regarding dilemma situations in which any decision alternatives are associated with human suffering, for example swerving to avoid a child and in the process risking your own life or that of other people. For a person, this is an ethical issue whereby he or she presumably would have had no more time at all to ponder in such a situation. You would have to program a machine so that it makes the right decision. This is an unresolved issue so far. Until it comes to this issue, however, it needs a better environment-sensing system and classification. The reliable detection of such a dilemma situation is not yet possible today.

Do we need new testing procedures for autonomous vehicles?
Winner: Definitely. Today, we test drivers when they get their driving licence or if they become conspicuous. And we test machines in their other functions. What counts is not that a car brakes at the right time, but that, if the driver jams on the brakes, the required breaking force develops. Highly complex testing procedures have been developed here in the course of many decades. These testing procedures are not, however, provided for testing artificial or machine intelligence or model-based perception.

So, how does Google regulate this problem, for example?
Wachenfeld: Even Google has no safety system so far which could compete with a human driver. They carried out test drives on highways in an initial trial period. Google's approach possibly changed due to the difficulty of proving safety. They are now testing vehicles at a maximum of 25 miles per hour. That is 40 km/h under constant surveillance. Under these conditions, twenty metres is enough visibility in order to come to a stop in good time. And they have a safety driver in the current testing phase. This is what is currently technically feasible.

Is this a realistic scenario?
Winner: Perhaps they will reach a speed of 60 eventually. You can actually reasonably cover all urban areas with that and this model is really interesting. The Google car is no replacement for a car really. Instead, a new mobility concept which combines minibuses with car-sharing is hidden behind this; it could be an alternative to today's form of public transport and one in which you would no longer require any roadworthy occupants.

Would this also be conceivable in Germany?
Winner: I would not rule it out. Only, there is no one developing it in this direction at the moment.

What is its current status in Germany then?
Winner: Vehicle manufacturers and system suppliers in Germany are very actively equipping their conventional vehicles with new autonomous functions without altering the mobility design. This is the fundamental difference to Google. The automotive industry in Germany intends building even better cars and superimposing another step onto the assistance systems which we have now.

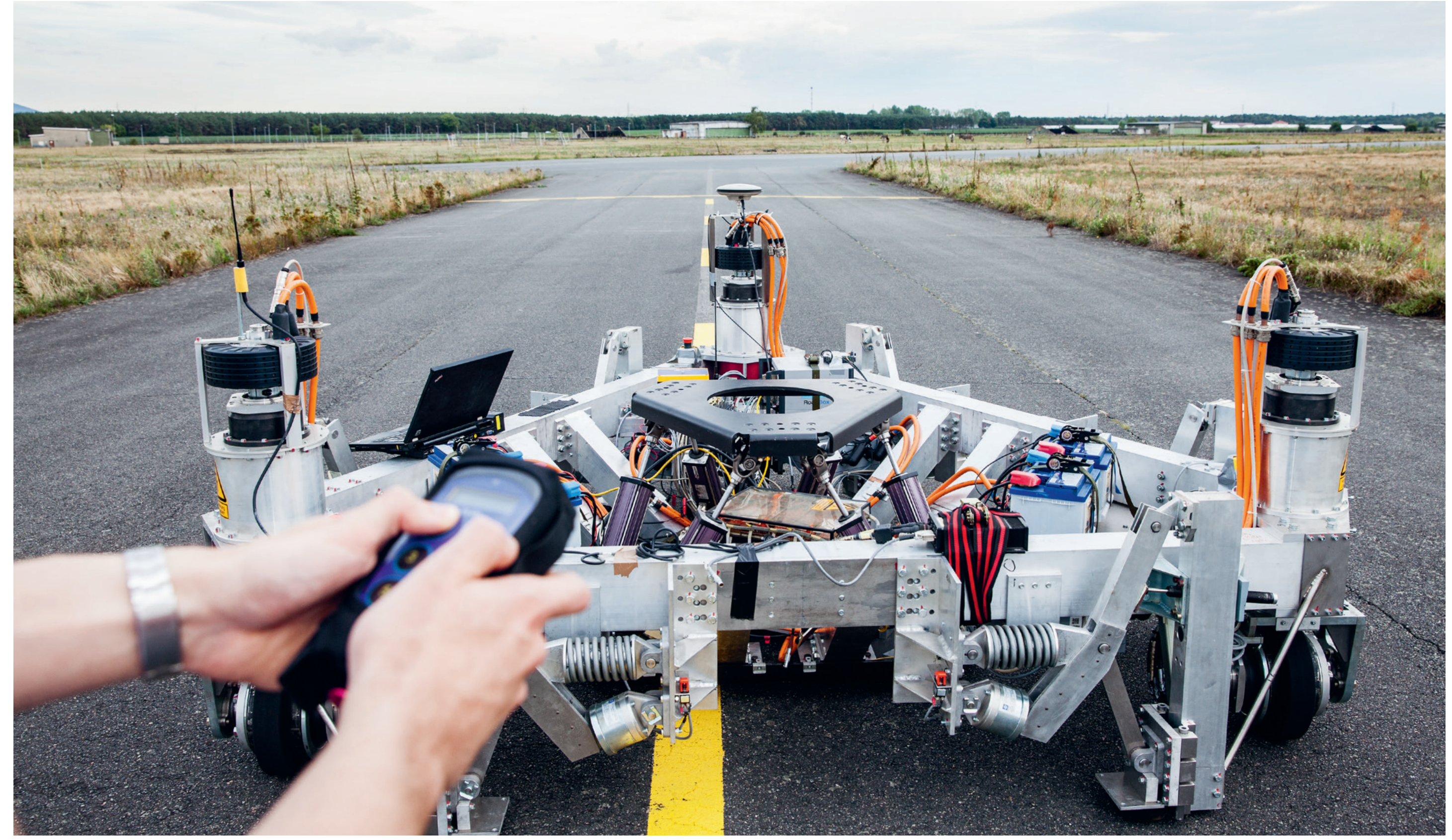

Photo: Sandra Junker

Developed at the TU Darmstadt and in the terrain test: Wheeled motion base driving simulator.

A "White Paper"
Autonomous driving – technical, legal and social aspects

Editors: Markus Maurer (TU Braunschweig, Institute of Control Engineering), J. Christian Gerdes (Stanford University), Barbara Lenz (German Aerospace Center Berlin), Hermann Winner, (TU Darmstadt, Institute of Automotive Engineering).

Springer-Verlag GmbH Berlin Heidelberg 2015
ISBN 978-3-662-45853-2
ISBN 978-3-662-45854-9 (eBook)
DOI 10.1007/978-3-662-45854-9

The edited volume funded by the Daimler-Benz Foundation highlights the topic of "Autonomous driving" in all its facets. The book is laid out in an interdisciplinary manner, depicts the current state of research, analyses the technical challenges and embeds the complex issues into the social context. Renowned academics from Germany and elsewhere examine mobility and transport issues, safety and insurance matters and legal issues as well as ethical questions and the relationship between man and machine: a well-founded and comprehensive overview of one of the major topics currently discussed by science, economics and politics in the course of digitalization.

Information

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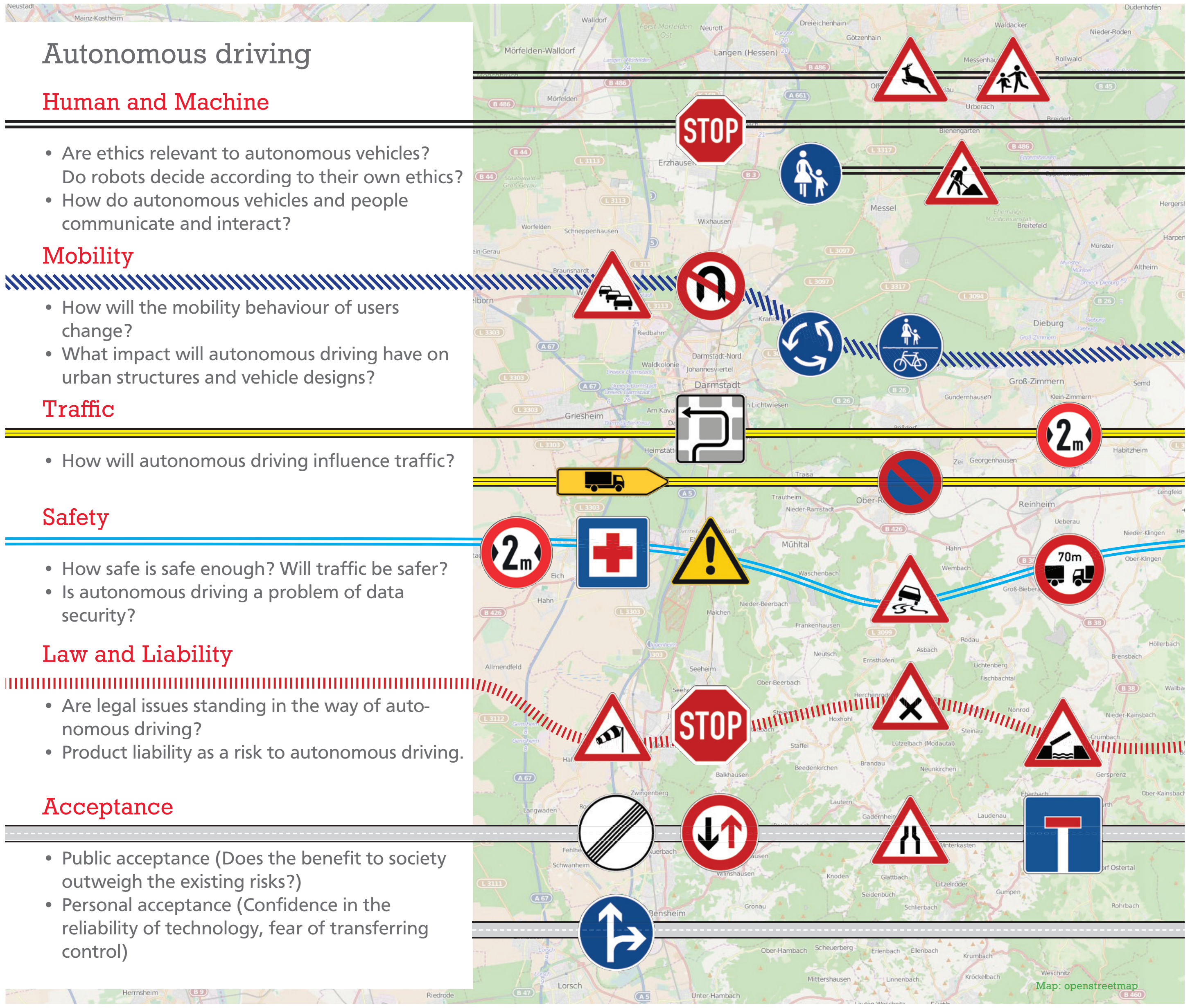

Figure: TU Darmstadt

Academic disciplines, but also society and politics still have to clarify numerous questions on autonomous driving.

Will autonomous driving turn the entire automotive industry on its head?
Winner: We can at least assume that suppliers will experience a boom: For example, Bosch needed about thirteen years for the first million radar sensors, then eleven months for the second and one million per one to two months is estimated for this year. So you can see the dynamics of the market. And, in the field of image processing new players might come along as in the software field.

Where precisely does autonomous driving actually bring added value?
Winner: Let's take the Google model once again: It would benefit people who are cut off from individual mobility today, for example people with a handicap or older people who can no longer drive. It could relieve mothers who provide their children's taxi service today. This would incidentally also make one or other second car superfluous. Then autonomous driving will offer new opportunities to provide vehicles, for instance with car-sharing. At the moment, it still takes a great deal of time to get to the car. Autonomous vehicles could be brought to precisely where people need them. If the availability of these vehicles is better organized and so their working life increases, this will not only be more profitable for the providers of these services, but could also reduce the number of vehicles on the road. And of course I will be able to organize my time in the vehicle as a passenger completely differently.

What does automated driving mean for vehicle designs?
Wachenfeld: We could change vehicle designs over this. There are two approaches at the moment. German car manufacturing is happening in a more evolutionary way. The vehicles are becoming ever more luxurious up to models in which you drive as in a sedan chair. The Google and car-sharing approach reduces the vehicle to a minimum and plainly and simply provides transport for a limited time.

Will we have to build cars differently in the future?
Wachenfeld: Not necessarily due to automation. There is currently an interior design for vehicles which is adapted to the driving task. It would be exciting to adapt the interior to what I would like to customize in a vehicle. Why should I not use my car as a mobile office, recreation area or even as a dining room on wheels? This is all conceivable, functions, but of course only provided that a fully-automated journey in advanced form is possible.

What is still lacking for this?
Wachenfeld: Above all, automatic driving intelligence. It is still a huge challenge to map environmental perception and understanding of a situation on a computer. The basic technologies and sensors such as radar and camera are available, but they must be significantly further developed. And the more flexibly they are used, the more they must exhibit an intelligent repertoire of actions from which we are still a long way off.

Do we need a new infrastructure for autonomous vehicles?
Winner: I don't think we will need any substantial changes. But it would be very good to enable a form of road vehicle communication with which known issues are further communicated. Nevertheless, people will not rely on the network for decisions which must be made at the last moment, but make them independently.

A lot of data is produced during this communication…
Winner: Data protection and privacy are not really a barrier to automation. Automated driving even offers an advantage. It represents the driving of a machine, not of a person. This means that less personal data will actually be recorded. But this doesn't mean that there won't be problems elsewhere. If Google provides you with such a vehicle, your privacy will be lost the moment you enter. Anyone who gets in there knows this. We cannot assume the acceptance of the user in the case of "classic" car brands. The data must very clearly serve a purpose there, for example, safety.

At the beginning, you mentioned a time span of thirty years. What will our road traffic look like then?
Winner: Not so very different from today at all. If we were to start selling the first autonomous vehicles now, then we will start somewhere with the Mercedes S-Class or the BMW 7 series. Then, it will take ten years until we have arrived at the Golf Class. By then, more than fifty per cent of them will have been sold, five more years have passed, and almost another ten years until more than fifty per cent are on the road. In short: We will really have to wait a long time until autonomous driving prevails so that road traffic noticeably changes.

The author is an academic journalist with a PhD in history.

Data and facts

Professor Hermann Winner has been head of Automotive Engineering (Fahrzeugtechnik – FZD) in the department of Mechanical Engineering at the TU Darmstadt since 2002. The doctor of physics is a member of the advisory board of the German Federal Ministry of Transport and Digital Infrastructure and on the scientific advisory board of the German Association for Road Safety. Winner has applied for 100 patents in the field of automotive engineering.

Walther Wachenfeld is a research assistant in the Institute of Automotive Engineering at the TU Darmstadt and will remain a project team member in the "Villa Ladenburg" College of the Daimler-Benz Foundation until the end of October 2015. Wachenfeld successfully completed his studies of Electrical Engineering and Information Technology with a specialization in Mechatronics at the TU Darmstadt. His doctoral thesis concerns providing evidence of the safety of automated vehicles.

Current FZD project: "Potenzialanalyse einer selbstfahrenden Bewegungsplattform für Fahrsimulatoren" ["Analysis of the potential of a wheeled motion base with respect to applications of driving simulators and further mobile robots"] launched just now as a project funded by the German Research Foundation lasting 3 years. It will examine the potential applications for a driving simulator with wheels, which should be used for the realistic driving simulation of urban traffic situations.